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Progress in Californium-252 Neutron Brachytherapy

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1. Introduction

The potential of using Cf-252 to treat cancer patients was first described by Shlea and Stoddard in 1965 as a source of neutrons using brachytherapy procedures [Stoddard, 1986]. In the late 1960's and early 1970's, the United States and England initiated human clinical trials of Cf-252 **n**eutron **b**rachy**t**herapy (NBT) for treating patients of various cancer types. These earlier trials treated only very few patients and were given up prematurely due to then emerging interest in accelerator-based **e**xternal **b**eam **f**ast **n**eutron **t**herapy (EBFNT).

In 1976, Dr. Maruyama, then at the University of Kentucky Hospital, began the NBT clinical trials with a focus on intracavitary treatment of advanced cervix and GYN cancers. During the fifteen year period (1976-1991) at Kentucky, Dr. Maruyama had treated several hundred cervical cancer patients and obtained successful results [Maruyama et al., 1991]. Based on the successful cervical cancer trials at Kentucky, Dr. Maruyama moved to the Harper Hospital of Wayne State University and intended to expand the NBT trials to include interstitial treatment of many other cancer types. The clinical trials at Harper, however, did not last long after Maruyama's unexpected death in 1995.

In parallel with the effort of Dr. Maruyama, several groups in Russia, Czech Republic, and Japan began studies and clinical trials. These groups met several times in USA in 1985, 1990, and 1997 and exchanged their experiences with NBT. Great efficacy has been found for cervix cancers of all stages but most notable for the advanced stage III and bulky IB cancers [Maruyama et al., 1997; Tacev, et al. 2003]. Endometrial adenocarcinomas and vaginal cancers [Maruyama et al., 1997] were also very curable with NBT. Various oral cavity cancers, recurrent tumors, radioresistant tumors such as melanoma, sarcoma, and glioblastoma were effectively treated by NBT [Vtyurin & Tsyb, 1986; Tsuya & Kaneta, 1986; Maruyama & Patel, 1991; Medvsdev et al., 1991; Stoll et al., 1991; Vtyurin et al., 1991a; Vtyurin et al., 1991b]. It was estimated by 1997 that approximately 5,000 patients have been treated with NBT. In 1999 China implemented its first NBT afterloading system (using Russian-made Cf-252 sources) to treat mainly cervical cancers. Presently 18 NBT afterloading systems have been installed in China, with approximately 20,000 patients treated. A latest report, based on the follow-up data of 696 cervical cancer patients treated with NBT, shows that the overall survival rate at 3 and 5 years are clearly better and that the late complications are lower than those treated with the conventional gamma-brachytherapy

[Lei et al., 2011]. While there is no standard treatment regimen exists for NBT, an overwhelming majority of the clinical studies were based on a mixed treatment method of which NBT is implemented first and then followed with the traditional external-beam radiotherapy (EBRT) .

While much progress has been made in intracavitary NBT over the years, currently there is no clinical implementation in interstitial NBT. The major obstacle for interstitial NBT has been that either the size of the Cf-252 source was too big or the activity was too low. In a review article [Maruyama et al., 1997], which was published after his death, Dr. Maruyama stressed the need for developing small size high activity Cf-252 source seeds and afterloading machines to facilitate clinical trials on the interstitial treatment of brain tumors, sarcomas, and a large variety of tumors. With this mission in mind, Isotron Inc. (a start-up company in Alpharetta, Georgia, USA) in 1999 entered a 5-year corporative research and development agreement (CRADA) with the Oak Ridge National Laboratory (ORNL) of the U.S. to develop a new generation high activity miniature source seeds. In October 2002, under the CRADA, ORNL/Isotron successfully encapsulated a batch of new Cf-252 source seeds with size and activities suitable for interstitial NBT [Martin, 2002]. The overall effort of Isotron of bringing interstitial NBT to full commercial stage, unfortunately, did not reach fruition due to financial difficulties.

While the methodology of ^{252}Cf-based NBT is the same as that of the conventional brachytherapy modalities (based on gamma-emitting isotopes such as Cs-137, Ir-192, I-125, Pd-103, etc.), i.e. to bring the source close to (or into) the tumor volume of a patient, the characteristic of neutron emissions and the associated radiobiological effect make the NBT unique.

2. Califronium-252 production and availability

The isotope of Cf-252 was first discovered in 1952 in the debris from uranium that had been subjected to intense neutron irradiation [Fields, 1956]. Early investigation showed that Cf-252 has a half-life of between 2 and 3 years and a significant branching fraction for decay by spontaneous fission, making it an especially compact source of neutrons. These desirable properties led to a sustained national effort of the U.S. to produce and recover macroscopic quantities of Cf-252. This effort began in late 1952 with irradiation of multigram quantities of plutonium-239 (or Pu-239) in the Materials Test Reactor (MTR) at the Idaho National Engineering Laboratory and culminated in the eventual recovery of purified microgram quantities of Cf-252 in 1958 at Lawrence Berkeley Laboratory [Mosley et al., 1972].

As the scientific interest in Cf-252 grew, the demand for the isotope quickly exceeded the supply. As a result, a National Transplutonium Element Production Program was undertaken to produce large quantities of Cf-252 and other transplutonium isotopes for the research community. This new program led to a large scale market evaluation program at the Savannah River Plant (SRP) and a smaller research effort at Oak Ridge National Laboratory (ORNL) beginning in the late-1960s. Since 1973, the western world's supply of Cf-252 (which is about two-thirds of the world's supply) is produced in the High Flux Isotope Reactor (HFIR) and recovered at the Radiochemical Engineering Development Center (REDC) at ORNL [Martin et al., 1997]. The rest one-third is produced at Russia's Research Institute of Atomic Reactors facility, and is used mainly by Russia and China.

Initially, Cf-252 was produced at HFIR/REDC from the neutron irradiation of Pu-242. By 1968, most of the Pu-242 had been irradiated and transmuted to curium-244 (or Cm-244). Continual irradiation and recovery of Cm-244 led to subsequent buildup of Cm-246 and Cm-248, which greatly enhances the yield of Cf-252. This is because fewer neutrons are required to produce Cf-252. A Cf-252 production cycle involves the irradiation of 11 to 13 targets for 6 to 8 months in HFIR, followed by four months of processing and recovery in the remotely operated and maintained hot cells at REDC. A recent production cycle completed at HIFR/REDC yields typically 200-300 milligrams of Cf-252.

In May 2008, the US department of energy (DOE) announced that it was terminating its transuranic waste research and defense programs, putting the continued supply of Cf-252 to the western world in question. In May 2009, industry users and Cf-252 source manufacturers reached agreements with DOE to privately fund the Cf-252 program through FY 2012 with expectations that production will continue beyond that year and that future irradiation campaigns will be conducted every two years [NIDC, 2011].

3. Evolution of medical Cf-252 source fabrication

3.1 Earlier sources fabricated at SRL

The medical fabrication techniques were first developed at Savannah River Laboratory (SRL) [Mosley et al., 1972]. In general, operations are conducted remotely in a heavily shielded hot cell. Palladium (or Pd) is deposited onto a fine precipitate of californium oxalate, $Cf_2(C_2O_4)_3$, in an aqueous solution. The Pd-coated particles are then dried, calcined to Pd-coated Cf_2O_3, pressed into a pellet of approximately 50% theoretical density, sintered to 1300 °C, pressed again to approximately 90% theoretical density, then pressed into a capsule of platinum-10% iridium alloy, and sealed as a billet. At SRL, draw dies were used to reduce the diameter of this billet to as small as 0.30 mm in diameter.

One or more of the encapsulated cermet wires produced at SRL were included in a much larger source, the Applicator Tube (AT), which was used by Dr. Maruyama and collaborators at the University of Kentucky for intracavitary (e.g. gynecological) treatment. Figure 1 shows the doubly encapsulated AT source assembly. As shown, the outside diameter and length are 2.8 mm and 23.1 mm, respectively. A newly made AT source typically contained 10 to 30 µg of Cf-252. As the AT sources are obviously too large to be used for interstitial treatment, smaller seed capsules (< 1.1 mm dia.) had also been made at SRL. These seed sources, however, only contained 0.5 µg of Cf-252, a quantity that is too small for any practical use [Mosley et al., 1972]. Accordingly, in his review article [Maruyama et al., 1997], Dr. Maruyama stressed the need for developing small size high activity seed sources and afterloading machines to facilitate clinical trials on the interstitial treatment of brain tumors, sarcomas, and a large variety of tumors.

The current NBT treatment in China is implemented via an afterloading system (referred as Neutron Knife) developed by Zurua Science & Technology Co. As mentioned, a total of 18 systems have been deployed. According to the information available on the website of Zurua, each newly loaded source typically contains up to 1 mg of Cf-252 provided from Russia. While the activities of these sources are significantly higher than that of the AT sources, the dimensions (3 mm in outside diameter and 11 mm in length) are much too big, and therefore, the Neutron Knife system is only suitable for intracavitary NBT.
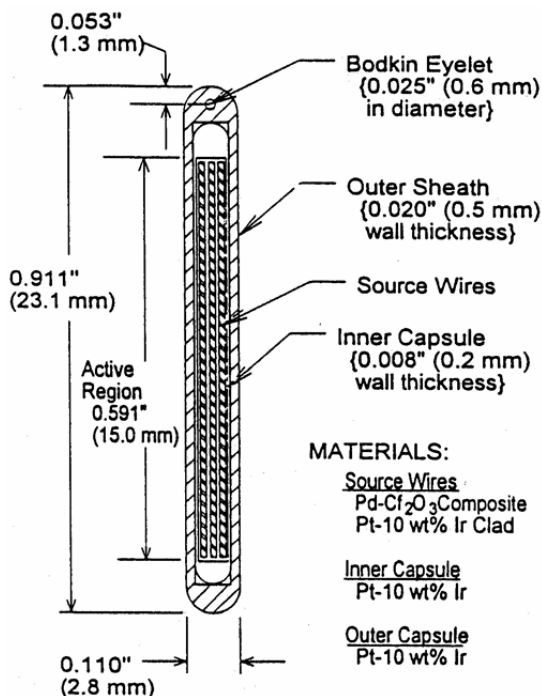
Fig. 1. The doubly encapsulated application tube (AT) source assembly

3.2 New high-activity miniature sources

It is worth noting that the active Pd-Cf$_2$O$_3$ "cermet" material included in the AT sources at SRL contains less than 0.1 wt% Cf-252. The REDC at ORNL have modified the SRL techniques to increase the Cf-252 content in the cermet material. Instead of sintering at 1300 °C, the pellet is heated to 1600 °C, which melts the Pd-Cf$_2$O$_3$ mixture. After cooling, the melted pellet is sufficiently strong and malleable to roll into a thin wire on a jeweler's rolling mill. For commercial sales, 1.1 mm square cermet wires are routinely fabricated with a nominal loading of 500 μg Cf-252 per inch (>0.1 wt% Cf-252) [Martin et al., 1997].

While the new procedure significantly increases the Cf-252 content (or specific activity) of the cermet wire, the high concentration of californium oxide necessarily degrades Pd workability. As a result, it was not possible to roll the cermet into a diameter below 0.6 mm, the size needed to make sources for interstitial treatment. In 1999, under a CRADA with Isotron, Inc., the ORNL developed a new wire shaping method that uses a modified swaging technique. That is, the wire is fed through a "shaper" unit, in which pneumatically activated collets hammer the circumference of the wire [ORNL, 2002]. A wire diameter of < 0.6 mm with uniform cross-section was obtained after repeated hammering at pressures between 40 and 100 psia. In October, 2002, a batch of seven high activity miniature source seeds was successfully encapsulated (Figure 2). The outside dimensions of the source capsule are 1.1 mm in diameter and 8 mm in length. The active length of the source is 5 mm. It is singly encapsulated with the wall thickness of 0.2 mm. The wall is made of platimum-

10% iridium alloy. The average quantity of Cf-252 in each source seed was approximately 90 μg, which is 200 times of that in the old SRL sources of a comparable size. The single wall and the small wall thickness cause the concern of structural integrity of the capsule wall. Specifically, the concern is about whether or not the capsule wall is strong enough to withstand the pressure build-up due to helium production from alpha decays [Rivard, 2000]. As of this writing, which has been more than three half-lives passed since the encapsulation, all seven sources show no compromise of their structural integrity. The small size of these new sources allow them to be used with remote high-dose-rate (HDR) afterloading systems comparable to current ones already in use for ^{192}Ir interstitial gamma brachytherapy. This new generation of source seeds thus made interstitial NBT practical.

One of the new sources was shipped to Georgia Institute of technology and National Institute of Standard Technology (NIST), where measurements were made on both neutron and gamma-ray dose profiles as well as the absolute total neutron intensity. Detailed discussion on the measured results associated with the new source is provided in Section 6. As of this writing, no commercial HDR unit has been built employing the new source for NBT. As mentioned in Section 1, all the HDR units developed in China employ the much larger Cf-252 sources supplied from Russia.
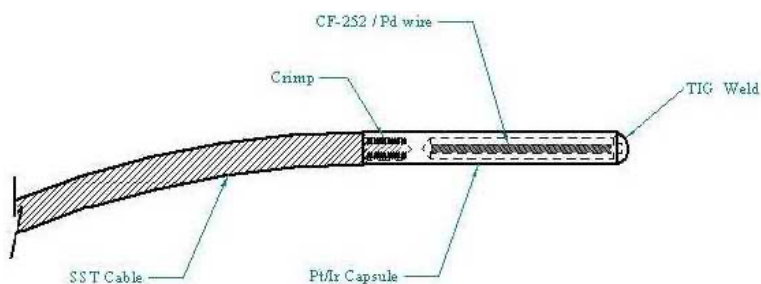

Fig. 2. The singly encapsulated new miniature source assembly

4. Biological basis of Cf-252 neutron brachytherapy

4.1 Neutrons and gamma rays and their interactions with tissue

Neutrons and gamma rays are often referred to as "indirect" ionizing radiations. Ionizing radiations consist of particles that are energetic enough to produce ions, break chemical bonds and alter biological function. Exposure to such radiation, therefore, can cause molecular and cellular changes such as mutations and chromosome aberrations, which in turn, may lead to cell death. Energetic charged particles (e.g. electrons, protons, alpha particles, or carbon ions), are referred to as "direct" ionizing radiations because they directly transfer their kinetic energies to a medium via Coulumb interactions with the atoms of the medium and cause ionizations (and excitations). Neutron and gamma rays are referred as "indirect" ionizing radiations because they must first interact with a medium to produce energetic charged particles, which will then cause ionizations/excitations in the medium. Gamma rays produce energetic charged particles (i.e. electrons) in a medium via atomic interactions such as photoelectric absorption, Compton scattering, or pair production. Likewise, neutrons produce energetic charged particles in a medium via nuclear interactions such as elastic scattering with the atomic nuclei, (n,p), and (n,α) reactions.

The radioisotopes that are commonly used in radiotherapy are mostly gamma emitters. These isotopes include Ra-226, Cs-137, Co-60, Ir-192, I-125, Pd-103, etc. Californium-252 is the only neutron-emitting radioisotope that has been used in radiotherapy. However, Cf-252 emits more than just neutrons. It also emits gamma rays, alpha particles, and beta particles (i.e. electrons). Because alpha particles and beta particles have very short ranges (< 1 mm), they usually do not penetrate the capsule wall of the source. As such, in a Cf-252 brachytherapy treatment, only neutrons and gamma rays emerge and interact with the surrounding tissue. As a rule of thumb, one third of the absorbed radiation dose in tissue surrounding a Cf-252 brachytherapy source is due to gamma rays and two thirds of the dose is due to neutrons [Rivard, 1999]. However, because neutrons (on the per unit dose basis) in average are a factor of 6 more effective in cell killing than the gamma rays, the biological effect of a Cf-252 brachytherapy treatment is overwhelmingly attributed to neutrons. The following subsection explains why neutrons are more effective in cell killing than gamma rays and how the biological effectiveness of Cf-252 neutrons is quantitatively assessed.

4.2 Relative Biological Effectiveness (RBE) of high-LET radiations

In general, the sub-cellular damages that bear biological consequences (e.g. cell death or transformation) result from densely packed ionization and excitation events taking place near or on a DNA molecule (or chromatin fiber). Sparsely distributed ionization/excitation events do cause DNA damages. But these damages are mostly mild and can be quickly repaired by the inherent enzyme-driven mechanisms of the cell. As such, one often relates the biological effectiveness of an ionizing radiation to a quantity called **l**inear **e**nergy **t**ransfer (LET), defined as the average amount of energy that is lost in a microscopic distance, e.g. one micrometer, approximately the size of a chromosome inside a cell nucleus. Gamma/x-rays and electrons are referred to as low-LET radiation because they produce sparsely distributed ionization/excitation events that give a low LET value (~0.3 keV/µm). Heavy ions (e.g. carbon-12 ions) and fission neutrons emitted from Cf-252, on the other hand, are referred to as high-LET radiation because they produce densely packed ionization/excitation events that gave high-LET values (>30 keV/µm). A high-LET radiation is more effective in cell killing than a low-LET radiation because the sub-cellular damage caused by the high-LET radiation is often too severe to be repaired correctly by the cell's inherent repair mechanisms.

The increased effectiveness of cell killing by high-LET radiations compared with low-LET radiations per unit absorbed dose is denoted by **r**elative **b**iological **e**ffectiveness (RBE). It is defined as the ratio of the dose of a standard photon beam (a 250 kVp X-ray beam or a Co-60 gamma-ray beam) to the dose of the test beam that is necessary to produce the same level of biological effect; i.e. it is an isoeffective dose ratio. In clonogenic survival assays, a survival fraction (SF) of 10% or 1% is often used as the "gold standard" for RBE estimations. As such, the RBE values vary with cell types. Clinically, the RBE values are estimated for both normal tissue reactions and tumor regression.

Other important considerations about the RBE values include:

1.   The RBE of a beam varies with the absorbed dose, generally increases at low doses. As such, the clinical RBE has been assumed to increase as the dose per fraction is reduced [Joiner, 2002].

2. The RBE of a low-LET beam varies much more markedly with the absorbed dose rate than the RBE of a high-LET beam.
3. The RBE of a test beam depends on the reference photon beam. The original reference beam was 250 kVp X rays, but for the purposes of radiation oncology, the standard is now Co-60 gamma rays [Kal, 1986].

4.3 RBE of Cf-252 brachytherapy sources

The RBE of the total (i.e. neutron + gamma ray) emission of a Cf-252 brachytherapy source has been obtained via both in-vitro and in-vivo experiments [Kal, 1986]. In these experiments, one irradiate the sample object (in vitro or in vivo) separately with a ^{60}Co gamma-ray source and a Cf-252 source and then compare the doses of the two sources that are needed to achieve the same biological effect. The following formula was used to determine the RBE for the total (i.e. neutron + gamma ray) emission of a Cf-252 source:

$$(RBE_{n\gamma})_{Cf} \quad = \quad \frac{(D_\gamma)_{Co}}{(D_{n\gamma})_{Cf}} \tag{1}$$

where $(D_\gamma)_{Co}$ and $(D_{n\gamma})_{Cf}$ correspond to the gamma-ray dose from the Co-60 source and the mixed neutron and gamma-ray dose from the Cf-252 source, respectively. The total biological effect of a Cf-252 source can also be expressed as the sum of the neutron effect and the gamma-ray effect. That is,

$$(RBE_{n\gamma})_{Cf}(D_{n\gamma})_{Cf} \quad = \quad RBE_n(D_n)_{Cf} \quad + \quad (D_\gamma)_{Cf} \tag{2}$$

where RBE_n is the neutron RBE, $\left(D_{n\gamma}\right)_{Cf} = (D_n)_{Cf} + (D_\gamma)_{Cf}$, which is the total dose from the Cf-252 source, and $(D_n)_{Cf}$ and $(D_\gamma)_{Cf}$ are, respectively, the neutron dose and gamma-ray dose of the Cf-252 source. Equation (2) simply says that the total effect is the sum of the neutron effect and the gamma-ray effect. An inherent assumption of equation (2) is that the RBE of Cf-252 gamma rays is unity, i.e. the effect of Cf-252 gamma rays is identical to that of the Co-60 gamma rays in equation (1). The combination of equations (1) and (2) gives the following formula for neutron RBE:

$$RBE_n \quad = \quad \frac{RBE_{n\gamma}D_{n\gamma} \; - \; (D_\gamma)_{Cf}}{(D_n)_{Cf}} \quad = \quad \frac{(D_\gamma)_{Co} \; - \; (D_\gamma)_{Cf}}{(D_n)_{Cf}} \tag{3}$$

Since the biological effect of gamma rays increases significantly as dose rate increases, both RBE_n and $RBE_{n\gamma}$ vary according to dose rate of the Cf-252 source. Table 1 shows the broad range of values of RBE_n and $RBE_{n\gamma}$ for Cf-252 for cells in vitro [Kal, 1986]. The broad range of values of RBE_n and $RBE_{n\gamma}$ were also obtained for in-vivo normal tissue reactions and experimental tumors [Kal, 1986]. Tables 2 and 3 show these values for normal tissues and experimental tumors, respectively.

While the values of RBE_n and $RBE_{n\gamma}$ obtained from in-vitro and in-vivo studies vary greatly among cell/tissue types and they also depend greatly on dose rate, the clinical RBE values of a Cf-252 brachytherapy source for treating a specific tumor are much better defined. The clinical

RBE values are usually determined by comparing the maximum tolerable doses (MTD) of normal tissues under Cf-252 treatment to that under a conventional multifractional gamma-ray treatment. Tsuya et al initially considered the RBE_n to be 2.2-3.5; later changed to 5-7 [Tsuya et al., 1979]; Castro et al estimated a value of 6.5-7.5 [Castro et al., 1973]; Vallejo et al estimated the value to be 6.4 [Vallejo et al., 1977]; Paine et al used a value of 7.0 [Paine et al., 1976]. Vtyurin considered the RBE_n of mucous membrane, bladder and rectum to be 4.0-6.3 [Vtyurin, 1982]. For treatment of bulky tumors, Maruyama et al used 6.0 with the majority of tumors being of the cervix, vagina and uterus [Maruyama et al., 1983].

Biological system	Total dose rate (Gy h^{-1})	$RBE_{n\gamma}$	RBE_n
V79 cells	0.08		6.7
V79 cells	~0.135		3.9
V79 cells	0.18	3.5	5.9
CHO cells (5% SF)	0.15	5.1	6-7.1
HeLa cells	0.16	2.9	4
HeLa cells	~0.13		4.4
HeLa cells	0.20	2.2	2.7
T-1 cells	0.045-0.27		7.1
EMT-6 cells	0.05-0.27	5	3.0-5.3
CHL-F (prolif.)	0.013-0.052		8.7-20
CHL-F (1% SF)	0.05	5.9	9.2
CHL-F (1% SF)	0.02	9	14.3

Table 1. The values of RBE_n and $RBE_{n\gamma}$ for Cf-252 for cells in vitro.

Biological system	Total dose rate (Gy h^{-1})	$RBE_{n\gamma}$	RBE_n
Pig skin:			
Early reaction – moist desquamation	0.07-0.484		5.4-7.4
Early reaction – hair growth inhibition	0.12-0.13	5.7-7.2	8.5-10.8
Early fibrosis, vasculitis, muscle degeneration	0.04-0.08		3.8-4.6
Late fibrosis, vasculitis in rectum, cervix, bladder	0.04-0.08		6.6-7.0
Mouse:			
Early skin effects	3.6		1.54-2.32
Late skin effects	3.6		2.84-4.28
Jejunal crypt cells	0.44		4.9
$LD_{50/30}$	0.65		4.1
Bone marrow CFU	0.77		2.1-2.7
Bone marrow CFU	0.108		2.44
Bone marrow CFU	0.099		2.1
Testes	0.21	3.7	5.1

Table 2. The values of RBE_n and $RBE_{n\gamma}$ for Cf-252 for normal tissues.

Biological system	Total dose rate (Gy h^{-1})	RBE$_n$
Mouse fibrosarcoma	0.13	6.3
Mouse EMT-6	0.78	4.7-5.4
Mouse leukemic cells	2.4; 2.8	2.7; 3.8
Mouse ascite cells	0.27; 0.0694	5.2; 5.6
Nude mouse HeLa tumors	1.86	11

Table 3. The RBE$_n$ values of Cf-252 for experimental tumors.

In a Phase-I trial with Cf-252 used as the sole source of radiation in treating malignant brain tumors [Patchell et al., 1997], the MTD for the scalp and normal brain tissues are 900 cGy$_n$ and 1200 cGy$_n$ (i.e. cGy of neutron dose), respectively. One may obtain the neutron clinical RBE against a conventional **multifractional** (mf) gamma-ray treatment by replacing $(D_\gamma)_{Co}$ in equation (3) with $(D_\gamma)_{mf}$, the gamma-ray dose needed in a conventional gamma-ray treatment to achieve the same clinical effect. That is,

$$RBE_n \ = \ \frac{RBE_{n\gamma}D_{n\gamma} \ - \ (D_\gamma)_{Cf}}{(D_n)_{Cf}} \ = \ \frac{(D_\gamma)_{mf} \ - \ (D_\gamma)_{Cf}}{(D_n)_{Cf}} \qquad (4)$$

If one assumes that the total MTD to the normal brain in the Cf-252 treatment includes 2/3 neutron dose (i.e. 1200 cGy) and 1/3 gamma-ray dose (i.e. 600 cGy) and that 8000 cGy is the MTD of normal brain tissue in a conventional multifractional gamma-ray treatment [Leibel & Sheline, 1991], then the RBE$_n$ can be derived as follows:

$$RBE_n \ = \ \frac{(D_\gamma)_{Co} \ - \ (D_\gamma)_{Cf}}{(D_n)_{Cf}} \ = \ \frac{8000 \ - \ 600}{1200} \ = \ 6.2 \qquad (5)$$

The above value is another confirmation that RBE$_n$ of 6.0 is a good estimate to be used in treating a variety of tumors and that this value does not vary greatly among different types of normal tissues.

Lastly, radiobiological models have been developed to estimate the value of RBE for neutrons emitted from ^{252}Cf [Rivard et al., 2005; wang & Zhang, 2006; Wang et al., 2007]. These models are all based on the linear-quadratic (L-Q) formula for estimating cell survival fraction. One notable finding is that the cell survival fraction of a mixed irradiation of neutrons and gamma rays (e.g. the field produced by ^{252}Cf) is lower than the survival fraction of the cells irradiated with neutrons and gamma rays separately. The additional cell killing effect is attributed to the interactions between the sublethal lesions produced by the two different radiation types. It was suggested that the use of L-Q model to directly evaluate the isoeffect of a mixed neutron and gamma-ray irradiation is superior to the employment of RBE$_n$ [Wang & Zhang, 2006]. This is because the L-Q model would eliminate the issue of what value of RBE$_n$ should be considered as most appropriate.

4.4 Other biological justifications of neutron brachytherapy

The large RBE of a high-LET modality alone, however, does not make it superior to the low-LET gamma-ray therapy modalities. In fact, a **t**herapeutic **g**ain (TG) exists only if the RBE of tumor response to the high-LET beam is greater than the RBE of normal tissue response. As such, the advantage of a high-LET radiotherapy (e.g. NBT) is most pronounced in treating: (a) locally advanced tumors containing high proportions of hypoxic cells (i.e. cells being short of oxygen), (b) slowly growing tumors containing high proportions of cells that are in the radioresistant phases, and (c) tumors proliferating too fast to benefit from the conventional 6-week 30-fraction scheme. These include a large variety of tumor types: locally advanced prostate carcinoma, head and neck tumors, soft-tissue sarcoma, cancer of the cervix, colon, rectum, and esophagus, melanoma, and malignant glioma. Clinically, however, only a small number of patients in a few tumor types have so far shown clear benefit from neutrons: locally advanced salivary gland tumor (which represents a small fraction of head and neck tumors), locally advanced cervical cancer, and locally advanced prostate carcinoma, bone sarcomas and soft tissue sarcomas [Maruyama et al., 1997; Debus et al., 1998].

The **t**herapeutic **g**ain (TG) of a high-LET modality over the conventional low-LET photon modality in treating hypoxic tumors is often evaluated via the **o**xygen **e**nhancement **r**atio (OER), defined as the radiation dose in hypoxic cells to that in aerated cells for the same biological effect:

$$\text{OER} \;=\; \frac{\text{Radiation dose in hypoxic cells}}{\text{Radiation dose in aerated cells}} \tag{6}$$

Most mammalian cell lines have an OER for cell killing of between 2.5 and 3 for photons [Kal, 1986]. It has been observed that the OER for Cf-252 irradiation is 1.4-1.6 [Kal, 1986]. If one takes the median values of the OERs, the potential therapeutic gain for ^{252}Cf NBT can be calculated as:

$$\text{TG} \;=\; \frac{(\text{OER})_{\text{photons}}}{(\text{OER})_{\text{Cf}-252}} \;=\; \frac{2.8}{1.5} \;=\; 1.87 \tag{7}$$

One of the obstacles that have hindered the progress of NBT was the late effect to normal tissues, which is believed to be more severe in all high-LET radiotherapy modalities than in the conventional x-ray therapy. That is, in the conventional x-ray therapy, much of the radiation damage to normal tissues is repaired during intermissions of the multi-fractional treatment scheme. In a high-LET radiotherapy, however, much of the damage to normal tissues is irreparable. This late-effect problem can be minimized by delivering superior dose distributions – i.e. large neutron doses to the tumor and small doses to the surrounding normal tissues. In fact, it has been shown that the late effect was significantly ameliorated among patients treated with the recently available multileaf collimators at several **e**xternal **b**eam **f**ast **n**eutron **t**herapy (EBFNT) centers [Lindsley et al., 1998]. In addition, Maruyama concluded that among his first group patients ten years after being treated with the Cf-252 AT sources, serious complications were less than 5% [Maruyama, 1986]. The latest clinical study in China based on 696 patients with cervical cancer also shows that the incidence of late complications due to NBT is much lower than that for patients treated with the

conventional brachytherapy using [192]Ir [Lei et al., 2011]. These evidences show that the late effect should no longer be an issue for patients treated with NBT.

 In addition to the dose distribution issue, one other clarification needs to be made on the differences between the EBFNT and the NBT. Both modalities are based on neutrons. However, the average neutron energy in EBFNT (~30 MeV) is more than an order of magnitude greater than the average neutron energy in NBT (~2 MeV). Since the LET of neutrons increases as neutron energy decreases, the difference in neutron energy translates to a factor of 5 in the difference in LET. In other words, the LET of NBT is approximately 5 times that of the LET of the EBFNT. As such, it is more appropriate to label the EBFNT as an intermediate-LET modality rather than a high-LET modality. The NBT, on the other hand, is a true high-LET modality. This difference in LET, in turn, translates to the differences in the clinical values of RBE (2-3 for EBFNT and 6-7 for NBT) [Kal, 1986] and OER (1.7 for EBFNT and 1.5 for NBT) [Kal, 1986]. Consequently, in comparison with the EBFNT, the NBT is more effective especially in treating hypoxic tumors.

5. Clinical data on neutron brachytherapy

Clinical trials involving NBT have been conducted in six countries during 1969-1997 to test the safety and efficacy of various protocols in an attempt to improve the therapeutic control of bulky, radioresistant tumors [Maruyama et al, 1997]. The resultant published data contains more than five thousand cases of patients treated in the United States, Russia, Czechoslovakia, Lithuania, Japan and England. During this period of research, twelve different groups, comprising more than eighty-nine physicians, physicists, oncologists and radiation biologists, conducted over sixty trials. Patients who participated in these studies were followed from two months to fifteen years to determine the overall clinical outcomes. In 1999 China became the first country taking NBT to the commercial stage, and has since treated approximately 20,000 patients with majority of them having cervical cancers [Lei et al., 2011].

Many of the early trials involving the use of Cf-252 brachytherapy attempted to determine the most effective scheduling protocol. Each group examined various dose schedules, with Cf-252 most commonly being used as an "early" or "late" neutron boost in conjunction with conventional external beam therapy. The validity of Cf-252 as a single modality was also researched. As a general consensus, all groups found Cf-252 to be extremely effective in causing rapid tumor regression in bulky, localized radioresistant tumors with large numbers of hypoxic cells. The effective regression of tumor size caused by Cf-252 results from the high-LET fission neutrons released during treatment. The sites in the studies included malignant glioma, gynecological tumors, cancers of the head, neck and oral cavity, gliomas. Each research group used sources of varying sizes and strengths depending on the location and year of source fabrication. Studies conducted in the United States and Japan used Cf-252 sources fabricated at the Savannah River Site (SRS) or Oak Ridge National Laboratories (ORNL). Studies performed in Russia, Czechoslovakia, and Lithuania used sources originating from Dmitrovgrad City, Russia.

5.1 Cervical treatment evaluation

Since the early 1970's, cervical cancer has been recognized as an ideal site for use of Cf-252. Because the ORNL "AT" source size is similar to that of existing photon sources such as Ra-

226 or Cs-137, it became a matter of substitution rather than whole design changes when it came time to use Cf-252.

Sixteen different groups in five different countries have carried out cervical cancer treatments with Cf-252 brachytherapy [Maruyama et al., 1997]. Various dose schemes, including a majority of trials that investigated the application of Cf-252 before ("early") and after ("late") external beam radiotherapy, were utilized in order to determine overall treatment efficacy. Other trials also examined the combination of Cf-252 and Co-60 or Ra-226. Patients were typically followed a minimum of two years with one trial following patients up to twelve years. Outcomes generally are cited in one of three groups, including tumor regression (TR), local tumor control (LTC) and survival rate (SR) with complications being sited when applicable. Survival rates for the use of Cf-252 throughout the various trials brought to light the fact that earlier stages of the disease had a higher degree of treatment success as compared to later stages. A definite advantage for the use of Cf-252 was also displayed over conventional gamma and external beam therapy in a majority of cases. Complications that have been observed through the course of these studies include, but are not limited to ulcerative cystitis, epithelitis, fistulas, rectal bleeding, rectitis, enterocolitis and hematuria.

A representative example of the trials that were conducted includes a study by a Russian group led by Marjina that treated 1,055 patients with stage I through III endometrial cancers from 1983-1996 [Marjina et al., 1997]. The study compared the efficacy of "early" and "late" application of Cf-252 in conjunction with external beam therapy and as a single treatment modality. The patients entered in the trial were followed for twelve years, with final results indicating that the LTC for "early" Cf-252 application was 87.2%, compared to 90.1% for "late" Cf-252 application and 79.4% for use of Cf-252 as a single modality. Five year survival rates were also determined for the three dose schemes, in which "early" versus "late" versus single application resulted in 86.5%, 86.3% and 56.1% respectively. Ten year survival rates for stage II versus stage III resulted in 71.6% and 66.6% respectively.

Another study by a Czechoslovakian group led by Tacev from 1986-1992 treated 430 patients with stage II and III cervical cancers examining the cumulative effects of Cf-252, Ra-226 and external beam therapy [Tacev et al., 1997]. Three dose schemes were utilized in which group: a) received 16 Gy of neutrons, 40 Gy of Ra-226 and 40 Gy of external beam therapy, group b) received 40 Gy of neutron, 16 Gy of Ra-226 and 40 Gy of external beam therapy and group c) simply received a conventional treatment regimen comprising 56 Gy of Ra-226 and 40 Gy of external beam therapy. Patients were followed for five years, with survival rates for groups a), b) and c) with stage II resulting in 89.8%, 83.7% and 72% respectively, and stage III resulting in 67.7%, 61.8% and 45% respectively.

An American group led by Maruyama at the University of Kentucky conducted the final representative study in which 218 patients with stage I, II and III cancer were treated by an "early" and "late" dose scheme in conjunction with external beam therapy from 1976-1983 [Maruyama et al., 1991]. Patients enrolled in the study were followed for up to ten years. Five year survival rates for stage I, II and III were 87%, 62% and 33% respectively, while ten year survival rates were 82%, 61% and 25%.

However, when the Cf-252 data from Lithuania and Japan are reviewed, one can see that the local control and survival rates are similar but complication rates are higher [Shpiklov et al.,

1991; Yamashita et al., 1991]. The apparent reason lies in the dose rates that were utilized in these centers. They were about 40% higher and/or were given on a more frequent schedule. The lower dosing schedules put forth early on at the University of Kentucky by Dr. Maruyama were not only efficacious, but had the highest level of safety as it related to complications.

The most important study is a randomized Phase III trial conducted by Tacev and colleagues from the Czech Republic [Tacev et al., 2003]. In that trial over 100 women with St IIb, IIIa, or IIIb received identical treatment with the exception that the initial brachytherapy was randomized between Cf-252 (6Gy-eq = 40 Gy) or CS/Ra. In this trial the 5 year local control (p< 0.00009), 5 year overall survival (p< 0.001) favored those receiving Cf-252. In addition there was no difference in complication rates between the two groups of patients. Clearly, Cf-252 had superior outcomes and yet had similar complication rates as Cs-137/Ra-226.

The above cited trials were conducted without use of chemotherapy, which has become a standard of care in the US. However, in 1993 the University of Kentucky group published on a cervical cancer Phase II trial in which both CDDP (50 mg/m²) and 5FU (1000mg/m²) were delivered with twice-daily radiation (120 cGy BID) and Cf-252 brachytherapy [Maruyama et al., 1993]. The equivalent doses to Point A (85 Gy) and Point B (60 Gy) are what is accepted for traditional photon brachytherapy source treatment. In that trial only 1 patient had a grade III/IV event, well below other institutional reports using similar techniques with photon irradiation alone. Again, there is strong evidence of efficacy and safety from the proper use of Cf-252 in the treatment of cervical carcinoma.

From February 1999 to December 2007, 696 patients with cervical cancer (Stages IB to IIIB) in China were treated with NBT in combination with external-beam therapy [Lei et al, 2011]. The NBT was delivered at 7-12 Gy per insertion per week, with a total dose of 29-45 Gy to reference point A in three to five insertions. The RBE value used was between 2 and 3. The whole pelvic cavity was treated with 8-MV X-ray external irradiation at 2 Gy per fraction, four times per week. After 16-38 Gy of external irradiation, the center of the whole pelvic field was blocked with a 4-cm-wide lead shield, with a total external irradiation dose of 44-56 Gy. The total treatment course was 5 to 6 weeks. The overall survival rate at 3 and 5 years for all patients was 76.0% and 64.9%, respectively. Disease-free- 3- and 5-year survival rates were 71.2% and 58.4%, respectively. Late complications included vaginal contracture and adhesion, radiation proctitis, radiation cystitis, and inflammatory bowel, which accounted for 5.8%, 7.1%, 6.2% and 4.9%, respectively. These results compare favorably to the results of patients treated with the conventional high-dose-rate photon brachytherapy using ¹⁹²Ir.

5.2 Head and neck treatment evaluation

The head and neck region covers multiple cancer treatment sites including esophageal, tongue, floor of mouth, lip, skin/soft tissue, buccal mucosa, oral cavity and oropharynx. Twelve different groups in four countries have carried out head and neck cancer treatments with NBT. A majority of dose schemes used in these studies combined NBT with conventional external beam radiotherapy, with a handful of trials comparing Cf-252 and Co-60. Patients were typically followed a minimum of two years with a few trials following patients up to ten years. Outcomes generally are cited in one of three groups, including

tumor regression, local tumor control, and survival rate with complications being sited when applicable. The following studies detail the dose schemes, the year of the study, and the overall results obtained during the follow-up periods for select trials that are a representative sample of the head and neck cancer treatment group.

The first clinical study was conducted from 1973-1986 by a Russian group led by Vtyurin that treated 488 patients with a variety of primary and recurrent stage T1-T4 head and neck cancers, including tongue, oral cavity, buccal mucosa, oropharynx, lip and skin/soft tissue [Vtyurin, et al., 1997]. The dose scheme utilized in the trial examined the use of Californium-252 before ("early") and after ("late") external beam therapy and also as a single treatment modality. Patients enrolled in the study were followed for ten years with three and ten year survival results for the various treatment sites being as follows: Primary Tongue=57.9%, 36.5%; Recurrent Tongue=47.9%, 29.1%; Primary Oral Cavity=54.8%, 32.3%; Recurrent Oral Cavity=41.1%, 17.6%; Primary Buccal Mucosa=56.2%, 37.5%; Recurrent Buccal Mucosa=No data available; Primary Oropharynx= 44.4%, 27.7%; Recurrent Oropharynx=46.2%, 30.7%; Primary Lip=92.3%, 82%; Recurrent Lip=59.2%, 25.9%; Primary Skin/Soft Tissue=77.8%, 61.1%; Recurrent Skin/Soft Tissue=86.3%, 22.7%.

A Lithuanian group led by Shpiklov conducted another trial from 1987-1989, in which 43 patients with stage I tongue and oral cavity cancers were treated using a mixed therapy regimen of Cf-252 and fractionated external photon beam [Shpiklov et al., 1991] . The results of the study showed a tumor regression rate of 63% for the tongue cancer and 83% for the oral cavity cancer.

5.3 Malignant glioma treatment evaluation

Chin conducted the first clinical study of using Cf-252 to treat malignant glioma at the University of Kentucky from 1980-1990 [Chin et al., 1991]. In this study, 85 patients were treated solely using single and multiple Cf-252 tubes and also in conjunction with external beam therapy. The overall median survival time with Cf-252 being used as a single modality was 12 months. The results obtained from the single Cf-252 tube in combination with external beam therapy at the eight month point had a survival rate of 87%, but rapidly decreased after that point. The multiple Cf-252 tubes in combination with external beam therapy however, were found to have a one year survival rate of 73%, with only a gradual decrease after that point indicating a definite advantage over single tube use.

Patchell et al continued Chin's work at Kentucky with an open ended Phase I trial (a dose searching study), to test the feasibility of NBT as the sole treatment modality, and to determine the maximum tolerable dose for the treatment of malignant gliomas [Patchell et. al., 1997]. The study was an open-ended dose escalation study. Radiotherapy was delivered using Cf-252 implants as the sole source of radiation with a dose escalation protocol to determine the maximum effective tolerable dose. A starting dose of 900 cGy$_n$ (i.e. 900 cGy of neutron, which is equivalent to about 5400 cGy of gamma-ray) was known to be well tolerated and was chosen as the starting point. Thirty-three (33) patients with histologically confirmed astrocytomas or glioblastoma multiforme were entered into the study. All patients had undergone previous debulking surgery. Three patients with newly diagnosed malignant glioma were entered at each dose step, and the number increased to six patients in dose steps at which necrosis of brain occurred. Ten patients developed scalp necrosis

associated with scalp doses above 900 cGy_n. The protocol was revised to limit the maximum scalp dose to less than 900 cGy_n. After this reduction, no additional patients developed scalp necrosis. The study ended when two patients at the 1300 cGy_n dose step developed radiation necrosis of the brain. In all, three patients developed brain necrosis outside the treatment volume (more than 2 cm beyond the lesion as determined by enhanced MRI scan), one at a dose of 1200 ncGy and two at a dose of 1300 ncGy. In every instance, the brain necrosis was confined to the area adjacent to the treatment volume, and the extensive necrosis seen after external beam neutron therapy was not present.

The clinical investigators concluded:

1. Neutron brachytherapy using Cf-252 as the sole source of radiation is a feasible treatment for malignant glioma;
2. The scalp tolerates less neutron radiation than the brain; and
3. The most tolerated dose (MTD) (and the recommended dose for a Phase II trial) of interstitial neutron brachytherapy is 1200 cGy_n.

Use of this starting point avoided ineffective doses while avoiding radiation necrosis in the first dose step. After a given dose step had been completed, the next escalation step was not started until the first patient treated in the previous dose step had completed neutron therapy and had been observed for at least 12 weeks. Each subsequent dose was increased by 100 cGy_n to 1300 cGy_n. For study purposes, the patients were followed indefinitely until they developed radiation necrosis of brain or died. Three to ten implant tubes (median, 6) with three to fourteen (median, 10) Cf-252 sources per implant were used. The median implant duration was 29.4 hours, with a range of ten to sixty-five hours. Early in the study, scalp necrosis was identified as an important complication. The median survival time was 10.9 months with five patients exhibiting no tumor recurrence at the time of death. Of these five patients however, three had radiation necrosis of the brain and two had infections associated with radiation necrosis of the scalp. The frequency of scalp necrosis throughout the study was noted as being higher than anticipated, with two possible explanations for the cause. The first explanation postulated, was the high fat content in the scalp region, which would have provided a high density of hydrogen atoms resulting in a higher neutron dose than other soft tissues. The second explanation was the inadvertent extension of the neutron implants beyond the margin of the brain to the level of scalp, which would have accounted for the higher dose observed and the resulting scalp necrosis. The early complication of scalp necrosis was subsequently controlled with careful treatment planning, and scalp doses were kept at less than 900 cGy_n.

5.4 Rectal treatment evaluation

Three different groups from two countries have carried out rectal cancer treatments with NBT on 64 patients at various times from the 1980's to 1990's [Burneckis et al., 1997; Sidorchenkov et al., 1997]. Multiple dose schemes were utilized depending upon the overall treatment strategy being used. Californium-252 was used in a mixed therapy regimen with external beam radiotherapy, as well as preoperatively as a single modality to enhance tumor regression. Results from the studies indicated a tumor regression rate of 83% in one study, with only anticipated complications arising in all three trials such as mild bleeding and minimal damage of proctal mucosa.

5.5 Hallmarks of performance

The clinical studies conducted to-date have consistently produced evidence to substantiate the following performance characteristics as hallmarks of NBT.

5.5.1 Single inactivation of cells

The neutrons of Cf-252 have very high LET. This means that a single event can inactivate the target site in the cell and lead to one-hit inactivation of cells. Clinical observations indicate high sensitivity and quick response of tumors to Cf-252 neutrons.

5.5.2 Absence of dose rate effect

Clinical studies show no dose rate effects. These results were expected based upon the one-hit survival curves of cells irradiated with Cf-252. The absence of dose rate effects allows Cf-252 therapy to be planned for a period of approximately 4 to 8 hours rather than the standard protracted and lengthy 48 to 144 hour schedules (at approximately 40 to 50 cGy per hour) used for photon radiation. Clinical observations show that there is little effect of varying dose rates in tumor response by Cf-252 studies to date.

5.5.3 Absence of sub-lethal (SLD) repair

One-hit survival curves of cells irradiated with Cf-252 mean little or no SLD repair occurs. No SLD repair is advantageous where neutron effects in the tumor result from Cf-252 sources implanted directly into the tumor. By avoiding or minimizing neutron radiation of adjacent sensitive organs, few complications were observed.

5.5.4 Late effect and leukemogenesis

Clinical trials have shown only about a 5% normal tissue complications have been observed after NBT with follow-up through 15 years. Further, there has been no occurrence of late leukemias, aplastic anemias, myelomas, or lymphomas observed. Secondary tumors in the lung or bowel are consistent with historical photon brachytherapy experience and do not present as an additional risk.

5.6 Summary of clinical results

Nearly 40 years of published clinical research of more than 25,000 patients treated in seven countries has demonstrated the viability of using Cf-252 NBT to treat cancerous tumors. Californium-252 NBT was found to be highly effective in causing rapid tumor regression in bulky, localized radioresistant tumors with large numbers of hypoxic cells. The effective regression of tumor size caused by Cf-252 is due to the high–LET nature of the spontaneous fission neutrons released during treatment. The absence of any new or serious side effects (when compared to photon brachytherapy) provides further argument that NBT is a viable alternative to, and an equal in performance to, photon brachytherapy. The five-year survival rates are equal to, and in some cases greater than, those seen with photon brachytherapy. It is reasonable to expect that the newly developed high-intensity miniature Cf-252 sources will improve dose delivery (over the large AT sources) and thus further improve the clinical outcomes of NBT.

6. Californium-252 propertiesand dose determination

6.1 Decay and emissions

Californium-252 has a half-life of 2.645 years. The majority, 96.9%, of [252]Cf decay is through alpha decay, but due to the short range these alpha particles do not escape the source capsule. A small, 3.1%, of [252]Cf decay is through spontaneous fission, and each fission produces two or three fission fragments as well as an average of 3.77 neutrons [Wierzbicki et al, 1997]. One µg of [252]Cf (0.536 mCi) emits 2.31 x 10^{6} neutrons sec^{-1} (approximately 2 percent overall uncertainty) [ICRU, 1977]. These fission neutrons have an energy spectrum that is often modeled as either a Maxwillian or a Watt fission spectrum, which peaks at 0.7 MeV and falls off rapidly at both higher and lower energies (see Fig. 3). The mean neutron energies inferred from reported measurements are between 2.13 and 2.15 MeV [Grundl & Eisenhauer, 1975; Walsh, 1991].
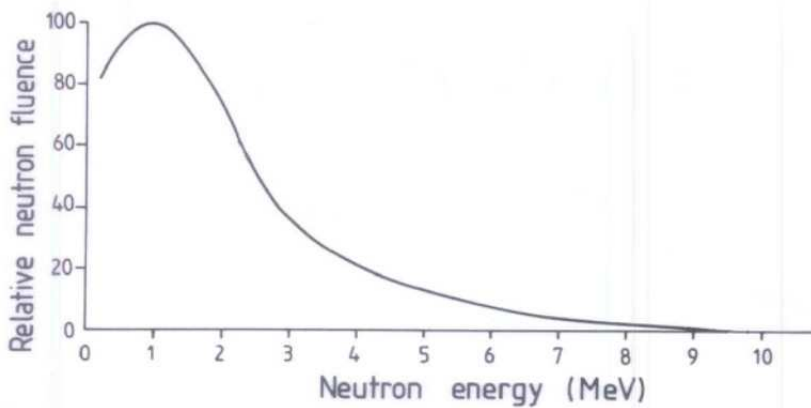

Fig. 3. Spectrum of neutrons emitted from spontaneous fission of [252]Cf.

Californium-252 also emits photons and beta particles. The photons emitted by Cf-252 (1 µg emits 1.32 x 10^{7} photons/sec) are roughly one-half equilibrium prompt fission gamma rays and one-half fission product gamma rays. Both components have mean energies of about 0.8 MeV, although their spectra are quite different. Unlike the fission product gamma-ray spectrum, which peaks near the mean energy, the prompt gamma-ray spectrum has a significant component above 3 MeV and increases exponentially with decreasing energy. Table 4 shows the gamma-ray energy spectra. The gamma-ray associated with alpha-particle decay is negligible (<0.1%). Because the fission products gradually builds up in a sealed Cf-252 source, one might expect that the absorbed dose of gamma rays relative that of neutrons emitted from the source would change with time. This, however, is not the case. The absorbed dose ratio was found to be a constant within a standard deviation of ±5% over a period of about three years [ICRU, 1977]. Given the 2.64 year half-life, any build-up of fission products is, therefore, unimportant.

In general, the beta particles (emitted from the fission products) and the associated bremsstrahlung x-rays do not penetrate the source capsule, and therefore, do not contribute to the external dose. However, for the new miniature sources having capsule wall thickness

of 0.2 mm, the bremsstrahlung x-rays do penetrate the source capsule and contribute significantly to the dose in the immediately vicinity of the source. Detailed discussion on the bremsstrahlung x-ray dose component for the new miniature sources is provided in Section 6.3.

Energy (MeV)	Gamma rays emitted from prompt fissions	Gamma rays emitted from fission products under equilibrium	Total
0.0-0.5	3.3×10^6	1.3×10^6	4.6×10^6
0.5-1.0	1.7×10^6	4.0×10^6	5.7×10^6
1.0-1.5	7.7×10^5	1.9×10^5	1.7×10^6
1.5-2.0	4.2×10^5	3.5×10^5	7.7×10^5
2.0-2.5	2.2×10^5		2.2×10^5
2.5-3.0	1.1×10^5		1.1×10^5
3.0-3.5	5.6×10^4		5.6×10^4
3.5-4.0	3.0×10^4		3.0×10^4
4.0-4.5	1.7×10^4		1.7×10^4
4.5-5.0	8.2×10^3		8.2×10^3
5.0-5.5	4.9×10^3		4.9×10^3
5.5-6.0	1.8×10^3		1.8×10^3
6.0-6.5	1.0×10^3		1.0×10^3
		Total = 1.322×10^7 photons μg^{-1} sec^{-1}	

Table 4. Spectra of gamma rays emitted from spontaneous fission and the fission products of Cf-252.

6.2 Dosimetry protocol

The absorbed dose of neutrons in tissue is mainly deposited by the recoil hydrogen nuclei (i.e. protons) from elastic scattering interactions. In average, a neutron transfers approximately half of its kinetic energy to a recoil proton in an elastic scattering interaction. After losing all its kinetic energy, the neutron is soon captured either by hydrogen via the $^1H(n,\gamma)^2H$ reaction or by nitrogen via $^{14}N(n,p)^{14}C$ reaction. As mentioned in Section 4, because the recoil protons deposit (or transfer) all their energies in tissue by producing short track (<100 μm) of densely packed ionization events, the absorbed dose of neutrons is referred to as being high-LET.

The absorbed dose of gamma rays in tissue is mainly deposited by the recoil electrons from Compton Scattering interactions. In average, a gamma photon transfers approximately one third of its energy to a recoil electron in a Compton Scattering interaction. After losing much of its energy in a few Compton Scattering interactions, the gamma photon is soon captured via a photoelectric absorption. As mentioned in Section 4, because the recoil electrons deposit their kinetic energies in tissue by producing long tracks of sparsely distributed ionization events, the absorbed dose of gamma rays in tissue is referred to as being low-LET. The rule of thumb is that roughly one-third of the absorbed radiation dose (Gy) in tissue near a Cf-252 source is due to low-LET gamma rays and two thirds is due to high-LET neutrons.

Since an effective brachytherapy treatment relies highly on accurate prescription of absorbed dose in and around a tumor volume, the objective of the NBT dosimetry protocol is to establish a method (or methods) that accurately specifies in detail the three-dimensional spatial distributions of absorbed dose rate in tissue-like medium (e.g. water) surrounding the source. The three-dimensional dose (or dose rate) distributions may be measured and calculated in a number of ways. The following subsections describe two different methods that were both used to obtain the detailed neutron and gamma-ray dose distributions surrounding a Cf-252 NBT source. Because the two methods are fundamentally different, their results should be complementary to each other. As such, the degree of agreement between the results may serve as a measure of the accuracy (or uncertainty) of the results.

6.2.1 The combined Monte Carlo and source strength measurement method

This method combines both the computational and the measurement results to obtain the dose distributions in water near a Cf-252 source. It first uses the Monte Carlo radiation transport code, MCNP-5 [J.F. Briesmeister, 2000], to calculate the normalized neutron and gamma-ray dose distributions in water (or tissue) nearby the source. It then uses a measurement method to obtain the neutron source strength (neutrons sec^{-1}) of the source. The absolute dose (or dose rate) distributions are then obtained by the multiplication of the two results.

A Monte Carlo radiation transport code is a computer-based method. It uses the known data associated with the radiation particles (e.g. neutrons, gamma rays, and electrons) and their interaction probabilities to simulate the random-walk behaviors of the radiation particles in the media. In a Monte Carlo code such as MCNP, the random-walk "history" of each particle is truly followed from birth to death. The information associated with a particle "history" at any moment throughout its lifetime includes particle type, energy, position, and direction. The absorbed doses at various locations (i.e. the dose distributions) in the media are obtained by tallying the statistics accumulated from a large number of particle histories. Based on today's computer speed (with a typical PC), it only takes a few minutes to run through millions of particle histories and to obtain results with statistical uncertainties of less than 1%. In addition, the MCNP code is the most widely used Monte Carlo code in the world for performing neutron, gamma-ray, and electron transport calculations, and therefore, both the algorithm and the data used in the code has been thoroughly verified and validated for its accuracy. Figure 4 shows the MCNP results of the neutron isodose contours normalized to 1 cm traverse the new miniature NBT source. The MCNP results have been compared with the previously obtained results and achieved good agreement [Rivard, 1999].

Since the MCNP results are normalized to a unit quantity of Cf-252 (e.g. 1 μg), to obtain the absolute dose rates one needs to multiply the MCNP results with the source strength (i.e. neutrons sec^{-1}) that can only be determined by measurement. The measurement method used at ORNL was based on three U-235 fission chambers surrounding the source. Each neutron emitted from the source has a fixed probability to be absorbed by a U-235 atom in one of the fission chambers, and thus produces a count. The measured neutron count rate of the source was then compared with the count rate obtained from a source of which the strength has been previously determined at the National Institute of Standard Technology

(NIST). The strength of the source was then derived from the measured count-rate ratio of the two sources.

The strength of a Cf-252 source determined at NIST is based on the Manganese Sulfate (MnSO$_4$) Bath Method [McGarry & Boswell, 1988]. In this method, the source is placed at the center of a large spherical tank, 1.27 m in diameter, containing MnSO$_4$ solution with a density of 1.37 kg liter^{-1}, until equilibrium of the Mn-56 activity is reached. This takes about 25 hours. The neutron emission rate of the source is determined by comparing the measured event rate of the gamma rays from the Mn-56 to that of the NIST standard source, NBS-I. The measured neutron emission rate (in neutrons sec^{-1}) is then converted to the Cf-252 content (in μg) using the conversion factor, 2.134 x 10^6 neutrons sec^{-1} μg^{-1}. The source strength obtained from this method has an uncertainty of 1.2%.
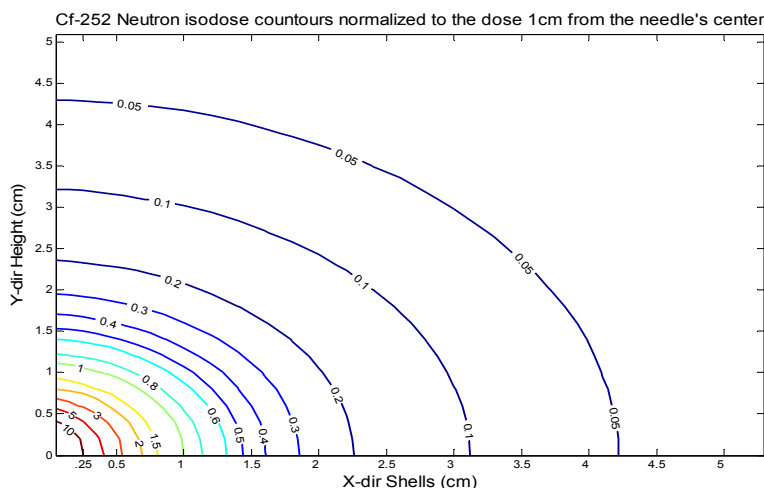
Fig. 4. Neutron isodose contours normalized as factors of the dose 1 cm traverse the source.

6.2.2 The two-ion chamber method

The most widely used method directly measuring both neutron and gamma-ray dose distributions in a mixed neutron and gamma field is the "two-ion chamber method". In this method, two miniature ion chambers having different neutron and gamma-ray responses are used to obtain neutron and gamma-ray doses separately [ICRU, 1977]. The two ion chambers commonly used are the T1 and M1 ion chambers made by Standard Imaging, Inc. Both chambers have the same geometry and a 0.056 cm^3 collecting volume. Of the two, T1 has high sensitivities to both neutrons and gamma rays, whereas M1 has a high sensitivity to gamma rays but a very low sensitivity to neutrons. The response of each ion chamber is related to neutron and gamma-ray doses D_n and D_γ by the following equations:

$$R_T^{'} = k_T D_n + h_T D_\gamma \tag{8}$$

$$R_M^{'} = k_M D_n + h_M D_\gamma \tag{9}$$

where the subscripts T and M refer to the ion chambers T1 and M1, respectively. Accordingly, $R_T^{'}$ and $R_M^{'}$ are the responses (i.e. the electric charge) of T1 and M1, respectively. The coefficients, k_T, k_M, h_T, and h_M, are the corresponding neutron sensitivities and gamma-ray sensitivities for T1 and M1. The values of h_T and h_M can be experimentally determined using a NIST-traceable Co-60 gamma-ray source, and the common unit used is nC/cGy. The values of k_T and k_M can be obtained by using the relative response curves available from ICRU-45 [ICRU, 1989]. One may then obtain the absorbed doses, D_n and D_γ, by solving equations (8) and (9) as:

$$D_n = \frac{h_M R_T^{'} - h_T R_M^{'}}{h_M k_T - h_T k_M} \qquad (10)$$

$$D_\gamma = \frac{k_T R_M^{'} - k_M R_T^{'}}{h_M k_T - h_T k_M} \qquad (11)$$

To obtain the dose distribution data for various positions near a Cf-252 brachytherapy source, one must conduct an in-phantom experiment with the two ion chambers, T1 and M1. In this experiment, the source is placed via a catheter tube located at the center of a Lucite-walled water phantom. The two ion chambers are placed under water at various locations and distances from the source to collect the electric charges. The electric charge data are then converted to the corresponding neutron and gamma-ray doses at various positions using equations (10) and (11). The spatial resolution of dose distribution is limited by the size of the ion chambers collecting volume, which is about 4 mm. This resolution is adequate for far away positions, but too poor for the nearby positions (< 2 cm from the source center point) due to the sharp dose gradients. For the nearby positions, one may use **t**hermo**l**uminescent **d**osimeters (TLD) or silicon diodes to measure the gamma-ray dose [ICRU, 1977].

6.3 Increased gamma dose in the new miniature source

A recent study of neutron and gamma dose profiles in water near a new miniature ^{252}Cf brachytherapy source reported discrepancies between the measured dose profiles and the dose profiles obtained computationally [Wang & Kelm, 2009]. The measured gamma dose rates near the source were found to be slightly greater than the neutron dose rates, contradicting the well established neutron-to-gamma dose ratio of approximately 2:1 at locations near a ^{252}Cf brachytherapy source of the old design [Rivard, 1999]. Specifically, the MCNP-predicted gamma dose rate is a factor of two lower than the measured gamma dose rate at the distance of 1 cm, and the differences between the two results gradually diminish at distances farther away from the source. These discrepancies were investigated and successfully explained by the effect of bremsstrahlung X-rays produced by the beta particles emitted from the fission products contained in the source. The well established neutron-to-gamma dose ratio of 2:1 works well for the old and large sources, but does not work for the new miniature sources. For the AT tube, the source capsule is thick enough that few bremsstrahlung photons can escape the capsule and contribute to the dose outside. For the new miniature source, however, because the capsule wall is so thin that many bremsstrahlung photons do escape the capsule wall and contribute significantly to the dose outside. Indeed, when one includes bremsstrahlung into the MCNP calculations, the gamma dose rates obtained from calculations agree well with the measured results [Fortune et al., 2011].

7. Dose prescription and treatment planning

Because the Cf-252 emission includes both neutrons and gamma rays and because neutrons are many times more effective than gamma rays (per unit dose) in cell killing, the quantity used for dose prescription is based on that of equation (12). The quantity is often referred to as gray equivalent, or $Gy_{eq.}$ That is,

$$Gy_{eq} = RBE_n \, D_n + D_\gamma \tag{12}$$

where D_n and D_γ are respectively the neutron dose and gamma-ray dose, and RBE_n is the relative biological effectiveness of neutrons with respect to gamma rays. In other words, Gy_{eq} is the equivalent amount of gamma-ray dose to achieve the same biological effect. As discussed in Section 4.3, clinical experience shows that RBE_n of 6 is a good choice for setting the maximum tolerable dose of normal tissues for many tumor types.

The method for dose delivery and treatment planning method can be directly borrowed from that of the existing Ir-192 high-dose-rate (HDR) remote afterloading systems with little modification. In other words, the treatment planning softwares such as BrachyVision of Varian and PLATO of Nucletron are directly applicable to NBT. The only modification needs to be made is the dose distribution data. That is, the gamma-ray dose distribution surrounding the HDR ^{192}Ir source will be replaced by the Gy_{eq} distribution surrounding the Cf-252 source. It should be noted, however, that the Gy_{eq} distribution are pre-calculated and pre-calibrated in water (see Section 6). The actual dose (in Gy_{eq}) to a tissue during a treatment will differ slightly from the dose to water. This is because neutrons strongly interact with hydrogen nuclei and because the hydrogen contents of tissues (especially fatty tissue) differ slightly from that of water. Table 5 shows the neutron dose at 1 cm from an AT source for various tissues including water [Rivard, 1999]. As shown, the neutron dose of most tissues is 6-8% less than that of water except that of fat, of which the neutron dose is 6% greater than that of water. The neutron dose to the bone is much less because the water (i.e. hydrogen) content is much less than that in other tissues.

Tissue Material	Neutron dose (cGy hr^{-1} µg^{-1})	Dose factor normalized to water
Water	2.064	1.000
Muscle	1.907	0.924
Brain	2.009	0.973
Skin	1.91	0.925
Fat	2.183	1.058
Blood	1.928	0.934
Lung	1.943	0.941
Bone	0.809	0.392

Table 5. Neutron dose at 1 cm from an AT source for various tissues including water [Rivard, 1999].

8. Boron-Enhanced Neutron Brachytherapy

Boron-enhanced neutron brachytherapy (BENBT) is a combination of neutron brachytherapy (NBT) and boron neutron capture therapy (BNCT). In a BNCT, a boron compound (a neutron capture agent) is first administered into the tumor of a patient. The tumor volume is then irradiated with slow (or thermal) neutrons. Each neutron capture reaction, $^{10}B(n,\alpha)^7Li$, releases an average of 2.4 MeV via short-ranged heavy ions, and therefore, is highly effective in killing the cell within which the reaction takes place. BNCT by itself, however, has not yet achieved notable clinical success mainly because it demands a perfect boron compound that can enter tumor cells with a high degree of specificity as well as a high concentration. The BENBT reduces that demand in that it is based on the already successful NBT with an additional boost of BNCT. No additional neutron irradiation is needed. The boost of BNCT comes from the same neutrons emitted from the ^{252}Cf brachytherapy source that are thermalized within the tumor volume.

In an experimental study [Wanwilairat et al., 2000] that employed a large water phantom (53 cm x 56 cm x 40 cm) with a 100-µg ^{252}Cf source (5.5 mm in active length and 3.3 mm in active diameter) placed at the center of the phantom, the results how that the relative ^{10}B enhanced dose increases linearly as a function of distance and reaches its maximum at 9.5 cm. If one assumes a ^{10}B concentration of 50 ppm, this maximum dose enhancement is translated to an increase of 28% of total dose. In another computational study [Rivard & Zamenhof, 2004], assuming a 15-cm-diameter brain phantom with a ^{10}B loading of 30 ppm and a tumor:healthy tissue ^{10}B ratio of 3:1, the results show that the biologically weighted dose enhancements are 0.6%, 6.5%, and 12.7% at 1, 3, and 5 cm (from the ^{252}Cf source), respectively. If one assumes that brain tumor recurrence is observed at 5 cm, then a 12.7% biologically weighted dose enhancement may be considered significant from clinical perspective. If new ^{10}B compounds were developed which could deliver greater tumor loading and tumor specificity, then BENBT would certainly become more clinically attractive.

9. Acknowledgement

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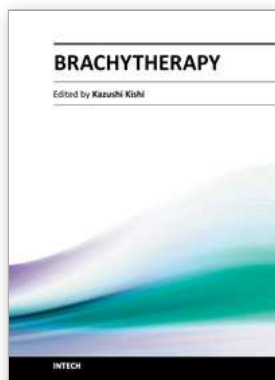
Brachytherapy

Edited by Dr. Kazushi Kishi

Importance of brachytherapy is currently increasing in cancer therapy. In brachytherapy each treatment is best fitted by physician's' hand, and appropriate arrangement and selection of radiation sources facilitates the fitting. This book is full of essences to make a breakthrough in radiation oncology by brachytherapy. I hope this book will encourage all people related. Contents 1: problem of currently popular dosimetric method; 2: Monte Carlo dose simulation of ruthenim-106/rhodium-106 eyes applicators; 3. Progress in Californium-252 neutron brachytherapy; 4. Clinical aspect of endobronchial brachytherapy in central airway tumor obstruction; 5. Review from principle and techniques of Iodine-125 production at nuclear reactor plant to their clinical practive in prostate cancer treatment; 6. Stereotactic Brachytherapy for Brain Tumors using Iodine-125 seed; 7. A brachytherapy procedure with organ-sparing hyaluronate gel injection for safe and eradicative reirradiation.

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